Claims

What is claimed is:

1. Use of an agent, wherein said agent is selected from

   i) an agent capable of inhibiting expression of a polypeptide belonging to the semaphorin family of proteins, and/or

   ii) an agent capable of inhibiting intracellular or extracellular proteolytic processing of a polypeptide belonging to the semaphorin family of proteins, wherein the agent is selected from antibodies or fragments of antibodies directed to said polypeptide, or fragments or variants of fragments of said polypeptide, and/or

   iii) an agent capable of inhibiting binding of a proteolytic fragment of a polypeptide belonging to the semaphorin family of proteins to a receptor and thereby inhibiting sequential activation of said receptor

   for the preparation of a medicament for prevention of progression of an invasive disease in an individual, wherein invasion of cells, other organisms or invasion of itself plays a role in disease pathogenesis.

2. The use according to claim 1, wherein the disease is selected from the group comprising autoimmune, infectious, growth disturbance, neurological, cardiovascular, respiratory, kidney or neoplastic diseases, with the proviso that the disease is not cancer.

3. The use according to claim 2, wherein the autoimmune disease is selected from the group comprising rheumatism, lupus erythematosus, systemic sclerosis, acrosclerosis, CRST syndrome, scleroderma, or rheumatic arthritis.

4. The use according to claim 2, wherein the infectious disease is selected from the group comprising tuberculosis, sepsis, HIV/AIDS, intestinal infectious diseases, meningitis, encephalitis, mycoses, or parasitic diseases.

5. Use of an agent, wherein said agent is selected from

i) an agent capable of inhibiting expression of a polypeptide belonging to the semaphorin family of proteins, and

ii) an agent capable of inhibiting intracellular or extracellular proteolytic processing of a polypeptide belonging to the semaphorin family of proteins, wherein the agent is selected from antibodies or fragments of antibodies directed to said polypeptide, or fragments or variants of fragments of said polypeptide, and/or

iii) an agent capable of inhibiting binding of a proteolytic fragment of a polypeptide belonging to the semaphorin family of proteins to a receptor and thereby inhibiting sequential activation of said receptor.

for the preparation of a medicament for prevention of metastasis of cancer *in vivo* and tumor progression *in vitro* and/or *in vivo.*

6. The use according to claim 5, wherein the cancer is lung, blood, breast, prostate, ovary, brain, kidney, lever, bladder, uterus, haemopoietic tissue, metabolic and endocrine system, epithelia, muscle, bone cancer, or cancer of unknown origin.

7. The use according to claim 6, wherein the cancer is lung cancer.

8. The use according to any of the claims 1-7, wherein the polypeptide of the semaphorin family belongs to the group comprising polypeptides of the subclass 3 secreted semaphorins or variants, or fragments, or variants of fragments thereof.

9. The use according to claims 1-7, wherein the polypeptide of the semaphorin family belongs to the subclass 3 secreted mouse semaphorins, or variants, or fragments, or variants of fragments thereof.

10. The use according to claims 1-7, wherein the polypeptide of the semaphorin family belongs to the subclass 3 secreted human semaphorins, or variants, or fragments, or variants of fragments thereof.

11. The use according to claim 9, wherein the polypeptide is mouse Sema3E having the amino acid sequence set forth in SEQ ID NO:1, or natural or synthetic variants, fragments, or variants of fragments thereof.

12. The use according to claim 10, wherein the polypeptide is human SEMA3E having the amino acid sequence set forth in SEQ ID NO:2, or natural or synthetic variants, fragments, or variants of fragments thereof.

13. The use according to any of the claims 1-12, wherein the agent capable of inhibiting expression of a polypeptide belonging to the semaphorin family of proteins is an antisense nucleotide compound of 19 nucleobases in length which specifically binds to a nucleic acid sequence encoding the semaphorin as defined in any of the claims 8-12, and inhibits expression thereof.

14. The use according to any of the claims 1-12, wherein the semaphorin of any of the claims 8-12 is cleavable by a serine protease *in vivo*.

15. The use according to claim 14, wherein the serine protease belongs to the family of paired basic amino-acid-cleaving proprotein convertase, comprising PC1/PC3, PC2, PC4, PC5/PC6, PC7/PC8, PACE4, or furin.

16. The use according to claim 15, wherein the serine protease is furin.

17. The use according to any of the claims 1-16, wherein the agent capable of inhibiting proteolytic processing of the semaphorin as defined in any of the claims 8-12 is a peptide fragment of said semaphorin, or variants thereof.

18. The use according to claim 17, wherein the peptide fragment of semaphorin comprises an amino acid sequence RXK/RR.

19. The use according to the claims 17 and 18, wherein the peptide fragment of semaphorin is a natural or synthetic contiguous amino acid sequence of at least 8 amino acids, such as for example a sequence of at least 12 amino acids, such as for example such as for example a sequence of at least 16 amino acids, such as for example a sequence of at least 20 amino acids, such as for example a sequence of at least 24 amino acids, such as for example a sequence of at least 28 amino acids, such as for example a sequence of at least 32 amino acids, such as for example a sequence of at least 36 amino acids, such as for example a sequence of at least 40 amino acids, such as for example a sequence of at least 44 amino acids, such as for example a sequence of at least 48 amino acids, such as for example a sequence of at least 52 amino acids, such as for example a sequence of at least 68 amino acids, such as for example a sequence of at least 84, such as for example a sequence of at least 100 amino acids, such as for example a sequence of at least 150 amino acids, such as for example a sequence of at least 200 amino acids, such as for example a sequence of at least 250 amino acids, such as for example a sequence of at least 300 amino acids, such as for example a sequence of at least 400 amino acids, such as for example a sequence of at least 500 amino acids derived from the sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 2, or variants of thereof, capable of binding a proprotein convertase and thereby inhibiting the activity of said convertase.

20. The use according to the claims 17, 18 and 19, wherein the peptide fragment of semaphorin comprises amino acid residues in a range of 30 to 50 amino acid residues of the sequence LARDPYCAWD GISCSRYYPT GTHAKRRFRR QDVRHGNAAQ QCFGQQFVGD (SEQ ID NO: 5), amino acid residues being numbered from the N-terminus of said sequence, such as 1-50 amino acid residues, for example 1-49 amino acid residues, such as 1-48, for example 1-47 amino acid residues, such as 1-46 amino acid residues, for example 1-45 amino acid residues, such as 1-44 amino acid residues, for example 1-43 amino acid residues, such as 1-42 amino acid residues, for example 1-41 amino acid residues, such as 1-40 amino acid residues, for example 1-39 amino acid residues, such as 1-38 amino acid residues, for example 1-37 amino acid residues, such as 1-36 amino acid residues, for example 1- 35 amino acid residues, such as 1-34 amino acid residues, for example 1-33 amino acid

residues, such as 1-32 amino acid residues, for example 1-31 amino acid residues, such as 1-30 amino acid residues.

21. The use according to the claims 17, 18 and 19, wherein the peptide fragment of semaphorin comprises amino acid residues in a range of 24 to 50 amino acid residues of the sequence LARDPYCAWD GISCSRYYPT GTHAKRRFRR QDVRHGNAAQ QCFGQQFVGD (SEQ ID NO:6), amino acid residues being numbered from the N-terminus of said sequence, such as 2-50 amino acid residues, for example 3-50 amino acid residues, such as 4-50 amino acid residues, for example from 5-50 amino acid residues, such as 6-50 amino acid residues, for example 7-50 amino acid residues, such as 8-50 amino acid residues, for example 9-50 amino acid residues, such as 10-50 amino acid residues, for example 11-50 amino acid residues, such as 12-50 amino acid residues, for example 13-50 amino acid residues, such as 14-50 amino acid residues, for example 15-50 amino acid residues, such as 16-50 amino acid residues, for example 17-50 amino acid residues, such as 18-50 amino acid residues, for example 19-50 amino acid residues, such as 20-50 amino acid residues, for example 21-50 amino acid residues, such as 22-50 amino acid residues, for example 23-50 amino acid residues, such as 24-50 amino acid residues.

22. The use according to claims 1 and 5, wherein the agent capable of inhibiting proteolytic cleavage of the semaphorin as defined in any of the claims 8-12 is an antibody or a fragment of an antibody, said antibody being raised against said semaphorin, or natural or artificial variants, or peptide fragments thereof, which specifically binds to and inhibits the cleavage of said protein by a serine protease *in vivo*.

23. The use according to claim 22, wherein the antibody recognises and binds to an epitope located within a sequence of about 5 to about 50 amino acids in length located in the structural domain of the semaphorin as defined in any of the claims 8-12, said domain comprising a proprotein convertase cleavage site RXK/RR.

24. The use according to claim 22 and 23, wherein the antibody is raised against a polypeptide having an amino acid sequence set forth in SEQ ID NO:1 or SEQ ID NO: 2, or variants or fragments thereof.

25. The use according to claim 24, wherein the antibody is raised against a peptide as defined in any of the claims 18-21.

26. The use according to any of claims 22-25, wherein the antibody is an isolated polyclonal antibody.

27. The use according to any of claims 22-25, wherein the antibody is an isolated monoclonal antibody.

28. The use according to claims 1 and 5, wherein the agent capable of inhibiting binding of a proteolytic fragment of a polypeptide belonging to the semaphorin family of proteins to a receptor and thereby inhibiting sequential activation of said receptor is a peptide fragment of the semaphorin as defined in any of the claims 8-12.

29. The use according to claim 28, wherein the peptide fragment is a contiguous sequence of at least 8 amino acids derived from the amino acid sequence set forth in SEQ ID NO: 3 or SEQ ID NO: 4 variants, or fragments, or variants of fragments thereof.

30. The use according to claims 1 or 5, wherein the agent capable of inhibiting binding of a proteolytic fragment of a polypeptide belonging to the semaphorin family of proteins to a receptor and thereby inhibiting sequential activation of said receptor is a peptide fragment of a receptor belonging to the Plexin family receptors, wherein said peptide fragment comprising a site for binding said proteolytic fragment, or natural or synthetic variants thereof.

31. The use according to claim 30, wherein the receptor is a receptor from the Plexin A subfamily of receptors.

32. The use according to claim 30, wherein the receptor is Plexin A1, Plexin A2 or Plexin A3.

33. The use according to claim 30, wherein the peptide fragment comprises a contiguous sequence of about 8 amino acids derived from the sequence of the ectodomain of the Plexin A1, Plexin A2 or Plexin A3 receptor comprising 1-542 amino acid residue of the sequence set forth in SEQ ID NOS: 11, 12 or 13, or natural or synthetic variants thereof.

34. Use of an agent, wherein said agent is selected from

i) an agent capable of inhibiting intracellular or extracellular proteolytic processing of a polypeptide belonging to the semaphorin family of proteins, wherein the agent is selected from antibodies directed to said polypeptide, or fragments or variants of fragments of said polypeptide, and/or

ii) an agent capable of inhibiting binding of a proteolytic fragment of a polypeptide belonging to the semaphorin family of proteins to a receptor and thereby inhibiting sequential activation of said receptor.

for the preparation of a medicament for treatment of malignant forms of cancer.

35. The use according to claim 34, wherein the agent is selected from

i) an agent capable of inhibiting expression of a polypeptide belonging to the semaphorin family of proteins, and

ii) an agent capable of inhibiting intracellular or extracellular proteolytic processing of a polypeptide belonging to the semaphorin family of proteins, wherein the agent is selected from antibodies directed to said polypeptide, or fragments or variants of fragments of said polypeptide, and/or

iii) an agent capable of inhibiting binding of a proteolytic fragment of a polypeptide belonging to the semaphorin family of proteins to a receptor and thereby inhibiting sequential activation of said receptor.

for the preparation of a medicament for treatment of malignant forms of cancer.

36. The use according to claims 34-35, wherein the agent is as defined in any of the claims 15-33.

37. The use according to claim 34-35, wherein the malignant cancer is carcinoma, melanoma, sarcoma, glioma, or blastoma.

38. An antisense compound of 19 nucleobases in length, comprising at least an 5-nucleobase portion of the sequence set forth in SEQ ID NO: 7 or SEQ ID NO: 8, capable of inhibiting expression of the semaphorin as defined in any of the claims 8-12.

39. A peptide compound as defined in the claims 17-21, capable of binding a proprotein convertase and thereby inhibiting the activity of said convertase.

40. An isolated polyclonal antibody compound as defined in the claims 22-25, natural or artificial variants thereof, or antibody fragments thereof, which specifically binds to an epitope located within a sequence of about 9 to about 50 amino acids in length located in the structural domain of the semaphorin as defined in any of the claims 8-12 comprising a proprotein convertase cleavage site RXK/RR, and thereby inhibiting the cleavage of said semaphorin at said cleavage site.

41. An isolated monoclonal antibody compound as defined in the claims 22-25, natural or artificial variants thereof, or peptide fragments thereof, which specifically binds to an epitope located within a sequence of about 9 to about 50 amino acids in length located in the structural domain of the semaphorin of any of the claims 8-12 comprising a proprotein convertase cleavage site RXK/RR, and thereby inhibiting the cleavage of said semaphorin at said cleavage site.

42. A peptide compound as defined in the claims 28 and 29 derived from the sequence of a semaphorin as defined in any of the claims 8-12, or variants

thereof, capable of binding the Plexin A1, Plexin A2 or Plexin A3 receptor without activating said receptor.

43. A peptide compound as defined in the claims 30 and 33 derived from the sequence of the ectodomain of Plexin A1, Plexin A2 or Plexin A3 receptor, or natural or synthetic variants thereof, capable of binding a polypeptide derived from proteolytic cleavage of the semaphorin as defined in any of the claims 8-12 by a proprotein convertase.

44. A method for producing an antibody raised against the semaphorin as defined in any of the claims 8-12, or natural or artificial variants thereof, or peptide fragments thereof, which specifically binds to an epitope located within a sequence of about 9 to about 50 amino acids in length located in the structural domain of the semaphorin as defined in any of the claims 8-12, comprising a proprotein convertase cleavage site RXK/RR, and thereby inhibiting the cleavage of said protein at said cleavage site.

45. A hybridoma cell line capable of producing a monoclonal antibody according to claim 41.

46. Use of the compound as defined in any of the claims 38-43, or combinations thereof for the prevention and/or treatment of metastasis of cancer *in vivo* and/or tumor progression *in vivo* and *in vitro*.

47. A method for diagnosis of malignant cancer, comprising

i) assessing the level of expression of the semaphorin as defined in any of the claims 8-12 in a tumor, and

ii) detecting fragments of the semaphorin as defined in any of the claims 8-12 in a body liquid, such as blood, urea or faeces, and

iii) measuring the ratio between a full length semaphorin as defined in any of the claims 8-12 and peptide fragments of said semaphorin in a tumor and/or a body liquid, such as blood, urea or faeces.

48. A method for prognosis of malignancy of cancer, comprising

i) assessing the level of expression of the semaphorin as defined in any of the claims 8-12 in a tumor, and

ii) detecting fragments of the semaphorin as defined in any of the claims 8-12 in a body liquid, such as blood, urea or faeces, and

iii) measuring the ratio between a full length semaphorin as defined in any of the claims 8-12 and peptide fragments of said semaphorin in a tumor and/or a body liquid, such as blood, urea or faeces.

49. Use of the compound as defined in any of the claims 38-43, or combinations thereof for the manufacture of a kit for diagnosis and/or prognosis of malignancy of a tumor.

50. Use of an agent capable of inhibiting proteolytic cleavage a semaphorin as defined in any of the claims 8-12, wherein said agent is selected the group comprising

i) a peptide as defined in claims 17-21, and/or
ii) an antibody or a fragment of antibody as defined in claims 22-25, and/or
iii) commercially available inhibitors of serine proteases and/or proprotein convertases

for inhibiting activation of a receptor of the Plexin A subfamily, comprising Plexin A1, Plexin A2 and Plexin A3 *in vivo*.

51. A method for producing an attractant polypeptide by establishing a cleavage product or a variant of a cleavage product from a repulsive polypeptide.

52. The method according to claim 51, wherein the attractant polypeptide is a cleavage product or a variant of a cleavage product of a semaphorin as defined in any of the claims 8-12.

53. The method according to claims 51 or 52, wherein the attractant polypeptide is a polypeptide having an amino acid sequence set forth in SEQ ID NO: 3 or SEQ ID NO:4, variants, or fragments, or variants of fragments thereof, established by proteolytic cleavage of Sema3E, comprising an amino acid sequence set forth in SEQ ID NO:1, variants, or fragments, or variants of fragments thereof, or SEMA3E, comprising an amino acid sequence set forth in SEQ ID NO:3, variants, or fragments, or variants of fragments thereof.